American Journal of Pharmacy

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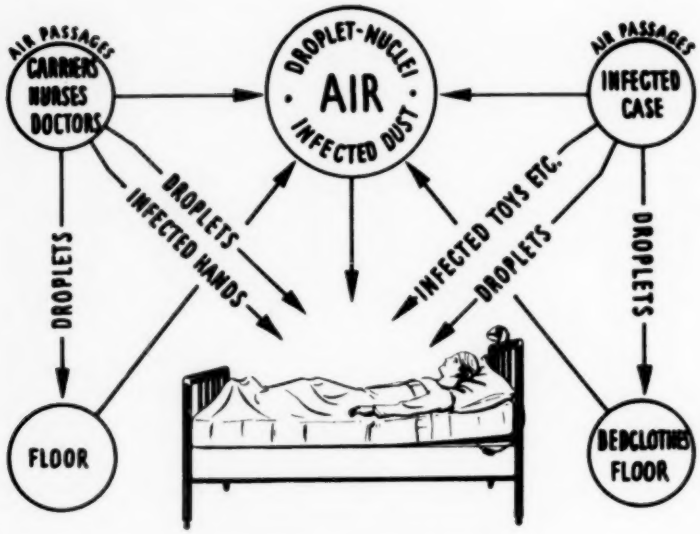

Environmental Sources of Infection
in the Hospital

(See article p. 86)

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CONTENTS

Editorial

The Need for Integration in the Organization of Pharmacy 84

Articles

Notes on Chemical Disinfection Relevant to Operating Room (O. R.) Activity. By E. G. Klarmann 86

Lipid Mobilizers and Their Role in Hyperlipemia. By E. E. Vogin 105

Selected Abstracts 117

E D I T O R I A L

THE NEED FOR INTEGRATION IN THE ORGANIZATION OF PHARMACY

ONE of the chief weaknesses in the organization of pharmacy is its lack of integration. Here, we do not refer to any need for racial integration although this, too, may be a problem in certain states. We are using the term "integration" to refer to a system whereby those engaged in the pursuit of pharmacy as a career would belong to their county, state, and national organization—all three a part of an over-all organization with a uniform purpose and program.

In the present scheme of things, there are large numbers of people engaged in some one of the broad avenues of pharmacy who cannot join the N. A. R. D. and would not be so inclined even if they could. The objectives of this organization are almost exclusively economic and have little or no professional inspiration. The truth is that it often appears that the stated objectives of this organization are almost diametrically opposed to the dictates of strictly professional reasoning. The A.Ph.A., on the other hand, is far too liberal in its qualifications for membership and uses almost no discernment in its selection of members. This organization has little if any motivation in protecting the economic interests of the practicing pharmacist and only too often has been rather feeble in its efforts to give him some such help and guidance. While on the surface it seems like a fine idea to let the N. A. R. D. look after the economic interests of pharmacy and the A.Ph.A., the professional, this has not worked out too well in practice.

To make matters still more confusing and the efforts of pharmacy still more impotent, some state and county pharmaceutical associations are affiliated with the N. A. R. D. and have a system of joint collection of membership dues while others are affiliated with the A.Ph.A. Still a third group of such state and local organizations feel no sense of allegiance at all and go their merry way—often in a direction completely opposite to the stated and official position of the national organizations. Then, too, we have all kinds of special or-

ganizations representing highly restricted groups in the field of pharmacy. Only too frequentiy, these completely autonomous groups are found "running with the ball" while the organizations which should be in the forefront sit perplexed, frustrated, and at times angered.

It is no wonder that many in government and industry and also the other health professions find it difficult to determine just what pharmacy's program is or is intended to be. When they seek to find out, they get a polyglot answer which often is so confusing and contradictory that they wished they had not asked.

We would suggest to the Secretary-Elect of the A.Ph.A., who will soon succeed to that office, that this—the over-all integration of the organization of pharmacy—should command top priority on his list of objectives. In spite of all claims to the contrary, our profession has not been gaining the recognition nor making the impact which it justifiably deserves. This can be changed, and we have sufficient confidence in some of the new leadership appearing on pharmacy's horizon to state categorically that it will be.

L. F. Tice

NOTES ON CHEMICAL DISINFECTION RELEVANT TO OPERATING ROOM (O. R.) ACTIVITY *

By E. G. Klarmann **

Terminology

SINCE the primary purpose of this presentation is to elicit questions from the audience, no attempt can be made to cover the area of "chemical disinfection" in complete detail.

It is deemed advisable first to suggest an agreement upon the meaning of certain terms which will be used in this discussion, also upon the classification of antimicrobial agents which are of significance to the O. R. picture; in addition, some general comments may be in order relative to the several types of available disinfectants, as well as to the verification of performance claims advanced on behalf of individual preparations.

Two of the more important terms to be considered here are "disinfection" and "sterilization" (1). Unless otherwise qualified, "disinfection" is carried out, as a rule, with the aid of a "disinfectant"; the latter term applies to a chemical agent which kills pathogenic microorganisms on inanimate objects, but not ordinarily bacterial spores. In contrast to this, "sterilization", as performed either by physical or by chemical means, is presumed to destroy all forms of life including resistant bacterial spores and also viruses; thus, the term "sterile" signifies freedom from any form of living matter whatever.

Two additional terms merit consideration in this connection. One is "antiseptic", a term which now enjoys a precise legal meaning by virtue of its definition in the Federal Food, Drug and Cosmetic Act; according to it, "antiseptic" and "germicide" mean the same thing except when the conditions of use are such as to involve prolonged contact with the body (as, e.g., in the case of an ointment, a dressing, etc.) in which case the term "antiseptic" may be applied to a substance capable of inhibiting the multiplication of bacteria rather than of killing

* Presented before the Operating Room Section of the New Jersey State Nurses Association, Atlantic City, N. J., October 30, 1958.

** Vice-President and Manager of Technical Services, Lehn & Fink, Inc., New York, N. Y.

them. The term "antiseptic" is used almost exclusively with reference to applications to the body or in body cavities.

The other term which has come into extensive usage in the recent past is "degermation" or "degerming action"; it signifies reduction of the bacterial skin flora through the action of certain antimicrobial agents (hexachlorophene, bithionol) usually incorporated in soaps or soapless detergents. Degermation is not synonymous with disinfection; actually the skin cannot be "disinfected" because it cannot be freed from all of the bacteria present upon it.

Finally, one should agree upon the meaning of the suffixes "-cidal" and "-static" as used respectively in terms such as bactericidal and bacteriostatic, tuberculocidal and tuberculostatic, etc. Briefly, the suffix "-cidal" denotes a capacity of killing, while the suffix "-static" indicates a capacity of inhibiting microbial proliferation, i.e., without a killing effect.

It might also be mentioned here that with respect to the meaning of some terms there exists no complete agreement. Thus it is argued occasionally that a "disinfectant" need not be tuberculocidal in action. However, it is felt that a product represented as a "hospital disinfectant" should certainly be capable of tuberculocidal action for reasons which are so obvious as to eliminate any need for discussion.

Selected Environmental Aspects of Infection

There are numerous indications to the effect that disinfection in the O. R. area should consider two aspects of entirely comparable importance, viz., environmental disinfection and instrument disinfection. As to the former, it is well known that contamination and infection of the surgical wound may originate with the environment if the premises, including the floors, furniture, and equipment, have been permitted to become depots of infection through contamination by infectious matter, sometimes with the unwitting help of the operating staff, i.e., doctors, nurses, and others. In this case, the anterior nares, or the skin, or both, may furnish the source of dispersal of pathogens which eventually reach the surgical wound. This may occur directly through some form of respiratory action (including speaking, coughing, sneezing, etc.), or through the agency of instruments and appliances contaminated in the course of their handling, or by the route of the "secondary reservoirs" particularly floors, blankets,

etc. from which the fomites are raised and distributed by air currents. In the case of structural faults or of incorrect ventilation, convection by air may also carry pathogens from other parts of the hospital into the O. R. area (2-6).

As is well known now, the problem of surgical infections due to pathogenic bacteria of environmental origin has become seriously aggravated through the emergence of antibiotic-resistant staphylococci. Because of this, it is neither safe nor proper to rely upon the prophylactic effect of antibiotics in view of the impressive record of acquisition by staphylococci of resistance to the different antibiotics which have been introduced successively in an effort to find *the one* antibiotic that would be active against all variants. Fortunately, several newer antibiotics are available which as yet have not been challenged by resistant staphylococci. However, it is only rational to demand that the use of such antibiotics should be reserved primarily for the *therapy* of staphylococcal infections; their availability for this vital purpose should not be jeopardized by any indiscriminate *routine prophylactic* administration. By the same token, renewed and heightened attention must be paid not only to correct aseptic technique, but also to a more effective control of the hazards of infection from environmental factors.

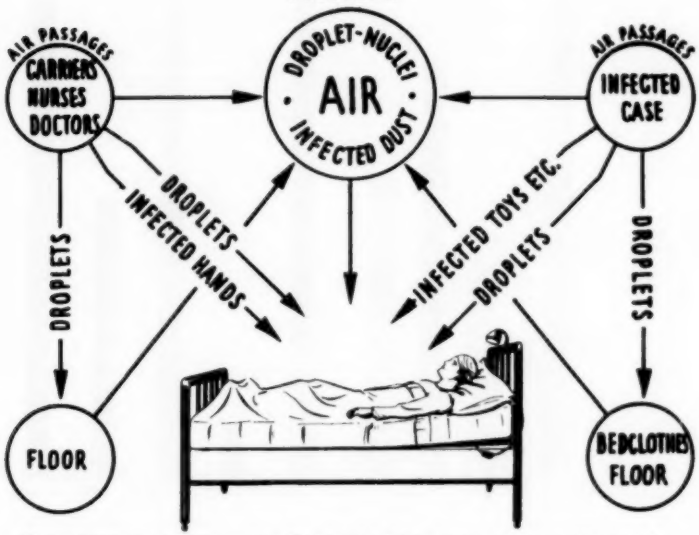
This is not deemed to be the proper place for a review of the fundamentals of integral asepsis, as it may be assumed that every O. R. nurse is fully familiar with this subject. As to its environmental aspect, this requires, among other things, regular, thorough disinfection of the O. R. premises. But attention must be paid also to the hospital as a whole in order to eliminate the possibility of microbial contamination of the O. R. area from sources (e.g., wards) located at some distance from it. Fig. I illustrates the many routes by which environmental infection can attack a ward patient; all of them are susceptible to control by a rational combination of environmental disinfection and aseptic technique.

In this connection, it should be noted that soap-and-water does not exhibit staphylocidal potency. It is essential that the disinfectant employed be possessed of an irreversibly *germicidal* (i.e., not merely inhibitory) effectiveness with respect to the *entire spectrum of pathogens involved in hospital infections, including staphylococci.* This requirement merits emphasis because, in spite of the great attention devoted to staphylococci, the existence of other pathogens involved

in endemic outbreaks must not be forgotten. By way of an example, reference could be made to the recurring problem of infantile diarrhea, caused by a pathogenic strain of *Escherichia coli* and spread by direct contact as well as by fomites of environmental origin. Another pertinent pathogen from the group of *Escherichiae*, viz., *Aerobacter aerogenes*, has been shown recently to be capable of developing a marked resistance to some antibiotics (*29*). A recent report mentions isolation and identification of *Pseudomonas* strains resistant to three of five antibiotics tested (*32*).

In addition, one might require that a hospital disinfectant should be capable of producing a residual antibacterial potential on disinfected surfaces, i.e., a capacity for the inactivation of sedimenting pathogenic matter for some time after and, ideally, between the applications of the disinfectant. This would be in keeping with a recent observation that the suppression of pathogens on disinfected surfaces has the adjunctive effect of lowering the microbial contamination of the environmental air (8). Thus, as a result of routine treatment of the floor of a post-operative recovery room with a synthetic phenolic disinfectant

FIGURE I.

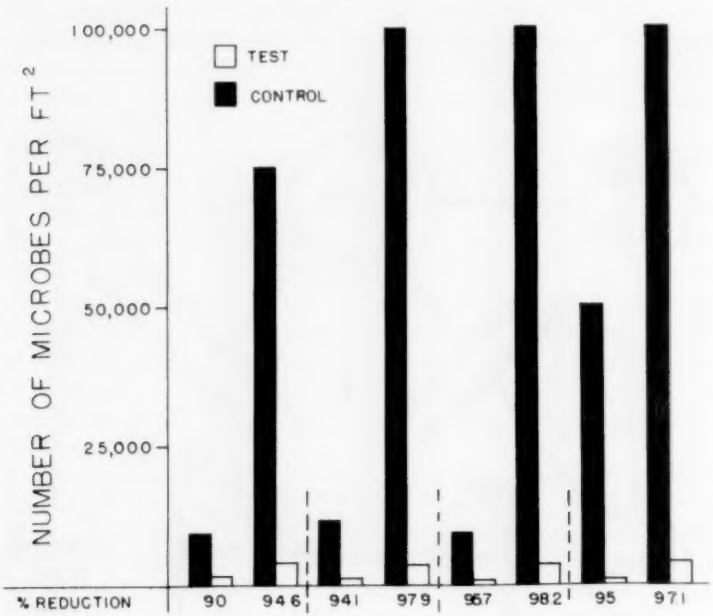


Environmental Sources of Bacterial (Including Staphylococcal) Infection on a Hospital Ward (Letourneau).

("O-syl") it was possible to keep its bacterial contamination reduced by over 90 per cent, in spite of the daily use of the premises by physicians, nurses, and attendants who were bringing in fresh contamination continuously. This is shown by Fig. II which indicates the drop in the number of microbes per square foot as determined by means of swab sampling. Even more significant is the observation that simultaneously the bacterial count of the environmental air space was being kept depressed by some 50 to 80 per cent owing to the decontamination of the floor area; this is illustrated by Fig. III.

A great variety of objects found in the hospital can and do become contaminated with infectious matter, thereby serving to transmit staphylococcal disease in one or another of its manifestations; however, particular attention should be paid to blankets which have been found on several occasions to carry a heavy load of contamination. Here,

FIGURE II.

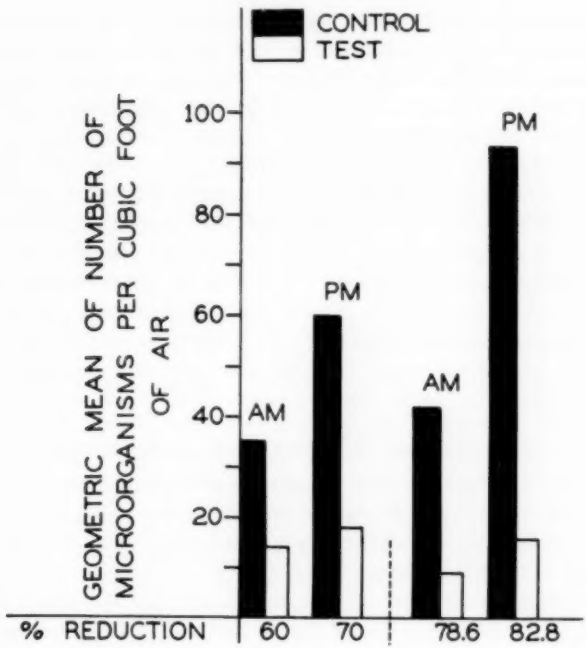


MAINTENANCE OF LOW BACTERIAL COUNT ON THE FLOOR OF A RECOVERY ROOM DUE TO ROUTINE DISINFECTION (DUNKLIN AND LESTER).

it should be emphasized that the low-temperature laundering process to which woolen blankets are usually subjected is not effective in ridding them of staphylococci. While the higher temperature plus chemical treatment employed in laundering bed linen may be assumed to have a sterilizing effect, this cannot be applied in the case of woolen blankets because it would cause shrinkage of the wool fibers. It is, therefore, deemed very important to realize that such blankets can be disinfected by chemical means easily and economically, as this serves to control a highly significant source of either direct or contributory environmental infection (9).

At this point, some reference should be made to the action of disinfectants upon antibiotic-resistant strains of staphylococci. Several such strains were subjected to tests on different occasions. The results

FIGURE III.



REDUCTION OF BACTERIAL COUNT OF THE AIR IN A RECOVERY ROOM DUE TO ROUTINE SURFACE DISINFECTION (DUNKLIN AND LESTER).

obtained indicate that staphylococci which have become resistant to several antibiotics fortunately do not acquire any increased resistance either to phenol or to the disinfectants tested whose staphylocidal efficacy has been established previously with the aid of standard strains (10, 31).

By combining these findings with those mentioned before, viz., the reduction of bacterial air contamination through the routine disinfection of surfaces, one arrives at the logical conclusion that the maintenance upon the critical surface areas (floors, blankets, furniture, shelves, etc.) of a residual antibacterial potential should aid in reducing the staphylococcal contamination of the enclosing air-space, thereby lessening the risk of air-borne infection by antibiotic-resistant staphylococci arising from their environmental depots ("secondary reservoirs").

To epitomize this portion of the discussion, it appears necessary for every member of the entire hospital staff to abandon the idea that, in controlling staphylococcal or other infection and cross-infection, any single factor should be regarded as the most important, or that taking care of one such factor at a time, while neglecting others, will solve the problem. It must be realized instead that, as a rule, there are several channels of transmission, all of which must be blocked, and this requires a coordinated effort on the part of the different hospital services including O. R., nursing, pediatric, housekeeping and laundry, at all echelons of each of them (33). This means also that a hospital which has had the good fortune of escaping the staphylococcal plague should consider itself just as open to the risk of an endemic invasion, as one who has become its victim. Thus, an early introduction of the required *concurrent* rather than of any *selective* preventive steps appears to be dictated by common sense.

Infection and Disinfection of Instruments

Microbial contamination of instruments and appliances occurs as a result of contact with the varied and ubiquitous sources of infected matter; this is why such objects must be sterilized or disinfected before touching susceptible exposed tissue.

Sterilization in the true sense of this term can be achieved with the aid of the autoclave, under the proper conditions of temperature and pressure prevailing for the required period of time, provided that the material to be sterilized is not damaged by exposure to these condi-

tions. More recently, sterilization by gaseous ethylene oxide has entered the picture. It provides (within certain limitations) a means of sterilization at low temperatures, thus lending itself for the treatment of a variety of articles which cannot tolerate exposure either to the hot steam of the autoclave or to the dry heat of the hot-air sterilizer (11). However, as yet there exists no chemical solution suitable for use with instruments, appliances and similar objects which, *acting at normal room temperature,* would assure results fully equivalent to those achieved by heat sterilization within a comparable period of time; or, to express it differently, no acceptable chemical disinfectant solution acting at room temperature should be relied upon to kill *resistant* bacterial spores within a period of time in which steam under pressure produces such an effect.

Among the most resistant bacterial spores of surgical significance are those of the *Clostridia* (such as *C. perfringens* or *C. tetani*). There is experimental support for the argument that spores of *Bacillus subtilis* (and probably of its variant *B. globigii*) are less resistant to chemicals (and incidentally also to heat) than those of the *Clostridia;* nevertheless, *B. subtilis* spores are employed frequently in tests aiming at verification of claims for sporicidal action. In the particular case of a "formaldehyde germicide", it was found that *B. subtilis* spores were killed hours earlier than those of three clostridial varieties which in some tests survived exposures of 8 hours to this germicidal material (12).

It is also noteworthy that in an experiment with *C. sporogenes* the different spore counts employed did not affect significantly the outcome of the test. This is shown in Table I. With spore counts

TABLE I

SPORE COUNT AND SPORICIDAL ACTION OF FORMALDEHYDE GERMICIDE (*Clostridium sporogenes*)

Number of Spores per Loop		*Result After*		*Number*
Calculated	*Counted*	*6 hours*	*8 hours*	*of Tests*
1,000,000	1,000,000	+	+	4
10,000	8,800	+	+	5
1,000	580-1300	+	+	14
100	80-85	6(+), 3(—)	4(+), 5(—)	9

ranging from approximately one million down to one thousand, survival was observed after eight hours in all tests; only when the spore count dropped to about one hundred did sterilization occur after 8 hours in some, but not in all cases. However, a 12 to 16 hour exposure might be adequate for sterilization, according to the experimental indications obtained.

Incidentally, the resistance of the test spores is further illustrated by their capacity of surviving the action of boiling water for as long as three hours. However, sterilizing action equivalent to that of autoclaving can be obtained by adding one of a group of suitable phenolic disinfectants to the boiling water as shown by Table II. The effectiveness of such solutions is due to the combination of chemical and heat action, the former being greatly accelerated and intensified at elevated temperatures (as is generally true of chemical reactions). Such information may prove useful in emergencies, or in places where autoclaves are not available.

What are the types of microorganisms found on contaminated surgical instruments and appliances? Most commonly, they are staphylococci and streptococci, also enterococci and coliform bacilli; other frequent contaminants are from the [illegible] and *B. proteus* classes. While *Pseudomonas aeruginosa* is not encountered often on surgical instruments, its presence should always be regarded as presumptive with respect to objects such as endoscopes (including bronchoscopes and cystoscopes), also oral instruments.

TABLE II

SURVIVAL OF *CLOSTRIDIUM PERFRINGENS* SPORES IN BOILING DISINFECTANT SOLUTIONS

Solution	Results of Exposure After					
	(per cent)	5 min.	15 min.	30 min.	2 hrs.	3 hrs.
Phenol	2	+	+	+	+	+
Cresol Comp. (U.S. Solution, obtained from [illegible])	2	+	+	+	+	+
[illegible] (obtained from [illegible])	2	+	+	+	+	+
[illegible]	2	+	+	+	+	+

Except for verified cases of infection with spore forming pathogens, resistant bacterial spores do not appear to be involved to a *major* extent in routine surgery. It should be noted, however, that this comment does not apply to surgery on the large intestines and on gangrenous tissue, nor to the treatment of wounds contaminated with earth or other matter suggesting the likelihood of invasion by spores.

More recently, the hazard of transmission of homologous serum hepatitis (known also as hepatitis "SH" or "B") has acquired considerable recognition in the hospital picture. This infection is conveyed not only by transfusions of virus bearing blood or blood products, but also by residues of infected blood remaining in hypodermic syringes and other instruments used previously on open or latent hepatitis cases. Actually, all procedures in which the skin or mucus membrane is broken by any non-sterile instrument carry the risk of transmission of serum hepatitis. Moreover, it is reasonable to assume that the same considerations apply to infectious hepatitis (also known as hepatitis "IH" or "A") since in this case, too, the causative virus occurs in the blood (as well as elsewhere). At this time, it is not certain whether either virus can be destroyed by any particular chemical germicide acting at room temperature. This is why autoclaving of instruments or boiling for a minimum of 30 minutes, preferably in the presence of a suitable disinfectant, should be the procedures of choice (13-15).

Importance of Cleaning

At this point, brief reference may be in order to a rather elementary subject which appears to receive but inadequate recognition, viz., the need for effective mechanical cleansing of the instrument to be disinfected, prior to its exposure to a germicidal chemical. It is quite obvious that under the actual conditions of microbial contamination pathogenic bacteria do not occur in pure culture, but rather in the presence of various forms of *organic matter*, such as blood, pus, mucin, vomitus, feces, and others. All of these substances display the tendency to react with and thus to inactivate (either partially or totally) the chemicals whose original purpose it is to enter into an irreversible reaction with pathogenic bacteria and, thereby, to bring about their ultimate elimination as a source of infection. The extent to which this interfering action of the organic matter present reduces the microbicidal potency of the disinfectants employed depends upon a number

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TABLE II

RESISTANCE OF *Clostridium sporogenes* SPORES TO BOILING DISINFECTANT SOLUTIONS

Disinfectant	*Dilution (per cent)*	*Results of Exposure After*				
		5 min.	*10 min.*	*15 min.*	*20 min.*	*30 min.*
Phenol	2	+	+	+	±	—
Cresol Comp. NF	2	+	+	±	—	—
Synth. phenolic (p.c. 5)*	2	±	±	—	—	—
Synth. phenolic (p.c. 10)**	1	±	±	—	—	—

* "O-syl".
** "Amphyl".

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of factors; other things being equal, however, the different classes of disinfectant agents differ greatly in their susceptibility to this impairment of their effectiveness. To illustrate, the disinfectant action of phenol or cresol would be impaired to a very much lesser degree than that of chlorine or of formaldehyde by the same amount and type of organic matter.

In any case, it would be inadvisable to attempt freeing a grossly contaminated instrument of pathogenic soil by direct exposure to a chemical disinfectant. However, even when observing the cardinal principle that cleaning should precede disinfection, one must still realize that the conditions will differ depending upon the type of instrument or appliance to be disinfected. Since a smooth surfaced object can be cleansed more thoroughly than, e.g., a hinged instrument, it is reasonable to expect that the latter will carry a greater amount of interfering organic matter after cleaning than the former. Some of this matter may settle in the form of a relatively deep layer in certain portions of the instrument; this would require gradual penetration by the bactericidal principle, thus delaying the disinfection of the object. Since it is only logical to facilitate rather than to hinder the action of the instrument germicide, the object to be disinfected should receive as much prior cleaning as can be applied conveniently. Occasionally, as, e.g., in the case of a sputum or mucus coated object, thorough wiping prior to immersion in the germicidal solution may mean the difference between adequate and inadequate disinfection, provided, of course, that the disinfectant has the inherent capacity of freeing the object of the pathogens with which it has come in contact; and this may include *M. tuberculosis* against which, unfortunately, some widely employed disinfectants are inherently ineffective (18).

What Is Effective Disinfection?

This is not deemed to be the place for a detailed discussion of the different testing techniques intended either to affirm or to negate the fitness of any particular germicide for the use or uses around the hospital for which it is being promoted. It is not uncommon to encounter controversial claims based upon bacteriostatic (inhibitory) action which has been mistaken for bactericidal (killing) action. Erroneous representations of this kind may be entirely unintentional; moreover, they may relate to the highly debatable question as to what constitutes bacterial death, short of the complete destruction of the

bacterial cell. While one cannot be concerned here with an elaboration upon this fascinating though complicated problem, it would be well to remember that for the purposes of hospital practice, a bacterial cell has ceased to be a source of actual or potential harm if, following exposure to disinfection, it is no longer capable of causing infection upon entry into a surgical wound or after settling on a susceptible mucous membrane, etc.; this may or may not coincide with the condition observed in the bacteriologist's test tube unless his technique is patterned closely along the lines of practical usage of the disinfectant studied.

The pragmatic interpretation of results of testing methods demands a rational approach in another direction as well. In endeavoring to simulate the conditions of practice, the bacteriological test nevertheless should involve an adequate safety factor; in other words, it is entirely proper to require that the disinfectant studied should be effective under test conditions which are exaggerated, as compared with those presumed to exist actually. (To use a simile, when asked to construct a bridge capable of carrying a 10 ton load, the builder will plan a structure presumably capable of carrying several times the specified load, as a factor of safety.) On the other hand, the exaggeration of these test conditions should not be so unrealistic as to place upon the disinfectant virtually impossible demands, i.e., with little or no bearing upon the conditions of its contemplated practical use, as this might result in the unjustified rejection or abandonment of a potentially valuable antibacterial agent (16).

At any rate, a "hospital disinfectant" worthy of this designation should exhibit a true broad-spectrum bactericidal effectiveness; in other words, it should be capable of killing all, and not just some, types of pathogens which are of significance in hospital practice and which are known to be susceptible to the action of chemical agents properly formulated and employed.

Some Instrument Germicides

Following is a brief discussion of several types of available instrument germicides (intended for use at room temperature):

Alcohol. Since ethyl alcohol exhibits marked bactericidal activity when employed in a concentration of 70 per cent or higher, it is important to avoid its dilution in use substantially below this range in

order to prevent a rapid loss of activity (17). In these high concentrations, alcohol causes coagulation of albuminous matter; consequently, thorough cleansing of the object to be exposed is indicated before immersion. (Isopropyl alcohol acts much like ethyl alcohol as an antibacterial agent.) Alcohol is not sporicidal, nor is it credited with a capacity for inactivating hepatitis virus.

Quaternary ammonium or cationic disinfectants ("Quats"). In recent years, some preparations from this class have gained considerable usage in the form of both their aqueous solutions and alcoholic tinctures. There is substantial evidence in support of the contention that their microbicidal potency has been overestimated at the time of their original introduction. A rather serious drawback from the hospital's point of view is that they cannot be relied upon for tuberculocidal action (18), and the same is true of their effect upon pseudomonads (19) and fungi (20). In combination with adequate concentrations of alcohol, they may yield a more satisfactory performance for certain purposes (e.g., preoperative skin preparation). They are not sporicidal, notwithstanding the occasional claim that prolonged exposure (of the order of 18 hours or longer) would cause spores to be killed (21). (According to some published findings, this will not take place even in several days.) Quaternary ammonium compounds are incompatible with soaps and with most soapless detergents; therefore, in order to prevent inactivation of their antibacterial power, any soap residue must be removed from all surfaces to which a quat is to be applied.

Inorganic and Organic Mercurials. In this class belong a number of antibacterial agents which may be regarded generally as being of an inhibitory rather than of a germicidal character. There is evidence to the effect that the action of mercurials can be reversed by various tissue fluids, including serum, blood, etc. Thus, an instrument apparently "disinfected" by exposure to the solution of a mercurial might be found to be contaminated after it has come in contact with a surgical wound; in this case, blood would cause the inhibited microorganisms to "revive" and to proliferate (22).

Some organic mercurials used as antiseptics in the form of tinctures (usually with alcohol and acetone) are more satisfactory owing to the adjuvant action of the solvent (23). Mercurials should not be depended upon for tuberculocidal, sporicidal, or virucidal action (24).

Formaldehyde. When used in adequate strength (of the order of 8 per cent), formaldehyde is actively germicidal. While it is also claimed to be sporicidal, some recent experiments tend to cast doubt upon its rapidity of action within a practical period of time, particularly when resistant spores are involved. With alcoholic formaldehyde (sometimes combined with hexachlorophene), sporicidal action may not be expected in every instance following an exposure of 8 hours or less, although it might be obtained after 12 to 16 hours (12).

Gaseous formaldehyde requires a high degree of humidity to exert its effect. So-called "formaldehyde cabinets" are not to be trusted as means of freeing instruments and appliances of their bacterial contamination.

Since formaldehyde is a strong coagulant, its use calls for thorough cleaning of the instruments prior to disinfection in order to avoid entrapment of the infectious microorganisms. The effectiveness of a formaldehyde solution as a virucidal disinfectant for instruments used in hepatitis cases has not been established, although its likelihood may be assumed.

Hypochlorites. Generally speaking, compounds which contain chlorine as active germicidal agent are corrosive for most metal instruments. The intense and non-specific reactivity of disinfectants based upon chlorine (or hypochlorite) is also one of their disadvantages in that it causes them to attack indiscriminately all forms of organic matter, and not alone that of pathogenic character. As a result, much of the germicidal power may be dissipated rapidly and uselessly where organic matter is present, little if any being left for attacking pathogens. Logically, therefore, this type of disinfectant should be employed only following complete removal of spills, blood, dejecta, etc. (25).

Iodophors. These are preparations in which elemental iodine is rendered soluble by means of suitable non-ionic or cationic surfactants (26). The affinity of iodine for organic matter may interfere with the inherent broad-spectrum germicidal quality of iodophors, although probably to a lesser degree than in the case of aqueous hypochlorites. The optimum of effectiveness of the iodophor type of germicide requires an acidity of the order of pH 3 to 4 in the working dilutions; at, or near neutrality (pH of 6 to 7), a three times higher

concentration would be necessary to produce a comparable germicidal effect. This rather high degree of acidity combined with the reactivity of the iodine may have a bearing upon the use of the iodophors on metal instruments which are subject to corrosion. Thorough removal of organic matter, also of any soap residues, is indicated prior to disinfection with iodophors in order to insure full germicidal activity.

Although the iodophors have been claimed to exhibit sporicidal, virucidal, and tuberculocidal activity in comparatively low concentrations, recent experiments indicate that substantially higher concentrations are required to produce these effects than those recommended originally (*27*). The practicality and economy of using such higher concentrations must be decided in every individual case.

Phenolic compounds. The prototype of this class of disinfectant is Saponated Cresol Compound NF (formerly USP). In spite of its broad-spectrum germicidal potency, this product has two serious disadvantages, viz., those of toxicity and irritancy; frequent objection has been raised also to its characteristic, pungent odor. More recently, certain synthetic phenolic preparations have become available which show substantially the same properties as Saponated Cresol Compound while being virtually free from its disadvantages. When used as directed, they exhibit broad-spectrum bactericidal and fungicidal action; in particular, they have the capacity of killing staphylococci, tubercle bacilli, also pseudomonads and pathogenic fungi (*28*). At room temperature, they do not destroy resistant bacterial spores, but they will do so in diluted aqueous solutions (of the order of 1 or 2 per cent) which are held close to or at the boiling point, within 20 minutes (incidentally, counteracting the rusting action of hot water) (12). Syringes and needles sterilized in this manner require rinsing with sterile water or saline in order to avoid systemic introduction of any disinfectant residues in the course of intravenous, intrathecal or other medication of a similar character. (In hard water areas, distilled or demineralized water should be used in the preparation of solutions for disinfecting or sterilizing instruments in order to counteract any tendency to clouding or precipitation).

As pointed out in the introductory comments, no disinfectant is completely unaffected by the presence of organic matter, and this applies also to the disinfectants of the phenolic class; however, as compared, e.g., with a hypochlorite or quaternary ammonium type of

product, a well-formulated phenolic disinfectant is likely to be impaired in its germicidal action to a relatively lesser degree.

Summary and Conclusion

It is held that chemical disinfection in the operating room area relates to two aspects of comparable importance, viz., environmental disinfection and instrument disinfection.

Environmental disinfection, properly performed (by means of a broad-spectrum germicide with residual antimicrobial action) may be logically expected to lessen the hazard of septic (including staphylococcal) complications of environmental origin, by suppressing the "secondary reservoirs" of pathogens on exposed surfaces in the operating room area and on contiguous premises, and thereby reducing the bacterial contamination of the surrounding air. To be truly effective, the environmental disinfection of the O. R. area must be coordinated with that of other hospital areas in order to prevent the transport of pathogens from the latter to the former.

Sterilization of instruments, in the true sense of this term, i.e., assuring destruction of *resistant* bacterial spores and of all types of viruses (including those of infectious and serum hepatitis), requires controlled exposure to steam or to ethylene oxide. Alternately, such sterilization can be produced by dilute solutions of certain phenolic disinfectants heated to the boiling point. Alcoholic formaldehyde, in adequate concentration, should produce a sporicidal effect at room temperature when permitted to act for 12 hours or longer; but no definitive information is available as to its effect upon hepatitis virus.

Disinfection of instruments (i.e., without assured sporicidal action) by means of chemical agents should imply a tuberculocidal effect. It is resorted to in the case of objects which would be damaged if exposed to heat. It calls for the removal of most of the organic matter by prior adequate cleaning. Instruments and appliances can be made safe for most O. R. uses by means of certain available disinfectant materials which are actually possessed of the required broad-spectrum microbicidal potency when applied in the proper concentrations and for the required periods of time.

It will be appreciated that, within the framework of this presentation, the subject of "chemical disinfection" could be treated only

perfunctorily, i.e., by reference to certain broad principles rather than by a discussion of specific problems. Moreover, it should be emphasized again that chemical disinfection alone will not solve the problem of bacterial, including staphylococcal infection or cross-infection, i.e., without proper attention to all the other factors involved in the transmission of contagion. As has been said by one of the speakers at a recent national conference on staphylococcal disease, "There is no one way in which staphylococci spread in a hospital and there is no one prophylactic method by which its spread can be prevented. The routes of infection are numerous and probably often devious and the precautions needed are many and complex. . . . Our preventive measures have therefore to minimize the endemic level, to prevent the emergence of epidemics, and to terminate epidemics when they occur" (30). *Integral asepsis* is the order of the day.

It should be evident that the selection of a chemical disinfectant for use in any area of hospital activity must not be treated as a matter of little consequence. According to valid indications, the control of one or more of the several possible routes of staphylococcal or other infection or cross-infection depends upon the rational selection and application of germicidal material. The conscientious manufacturer or supplier can play an important role in this picture by furnishing information not only regarding the advantages of his product, but also regarding its limitations. However, in the last analysis, it is up to the different authorized members of the hospital staff to make sure that the antimicrobial agents applied by them or under their direction will satisfy their respective missions. It is no exaggeration to say that informed choice and correct usage of such materials may mean the difference between health and sickness, or even between life and death.

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LIPID MOBILIZERS AND THEIR ROLE IN HYPERLIPEMIA

By Eugene E. Vogin *

ATHEROSCLEROSIS has been defined as a senile type of arteriosclerosis characterized by atheromatous degeneration of the walls of the arteries (1). Anderson (2) further states that atheromata are the result of lipid accumulation in the intima of the arterial wall. These lipid deposits consist of neutral fats, crystalline plates of cholesterol and doubly refractile masses of cholesterol esters. To further delineate the condition of atherosclerosis and explain the action of lipid mobilizers, it may be advisable to briefly review the metabolism of the ingested fats and the relationship of the products formed to atherosclerosis. Korn (3) has shown that hydrolyzed ingested fat is recombined in the intestinal mucosa and secreted into the lymphatic system in the form of triglycerides, which then combine with protein to form lipoproteins or chylomicrons. The lipoproteins thus formed have been separated by electrophoresis into alpha lipoproteins and beta lipoproteins. The former are high-density small particles while the latter are low-density macromolecules. Gofman and his associates (4) have proposed that the beta lipoproteins as a group may qualify as the atherogenic "agent". Ultracentrifugal separations have shown specifically that the beta lipoproteins exhibit Svedberg flotation (Sf) values between 12 and 100.

The belief that the lipids which accumulate in atheromata are derived largely from plasma is based upon the following evidence (5): (a) the demonstrated filtration of macromolecules through endothelium; (b) the isolation of serum beta lipoproteins from atheromata in man; (c) the chemical similarity between the lipids found in atheromatous plaques and those in serum; (d) the transfer of isotopically labelled cholesterol from serum to atheromatous lesions in man.

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The agents to be discussed include heparin and related compounds, estrogens and certain other steroids, thyroid hormones and the Lipid Mobilizer Factor (LM) of Seifter and Baeder (6).

The first observation of lipid clearing by heparin was reported by Hahn (7) in 1943. He showed that intravenous injections of heparin abolished alimentary lipemia in experimental animals *in vivo*. Since that time, much work has been done to elucidate the lipemia clearing action of heparin. Weld (8) found that heparin would clear alimentary lipemia not only in rats but also in dogs, cats, rabbits, and man. In an attempt to locate the site of this clearing action, he perfused heparinized lipemic blood through various body organs and concluded that no single organ was solely responsible, but that a widespread clearing action existed. A further observation made at the time was that the liver appeared to clear the blood slightly more than the other organs; however, the difference noted was too insignificant to provide conclusive evidence as to the liver being the primary site of action.

In 1948, Waldron and Friedman (9) observed that other anticoagulants of structure similar to heparin produced lipemia clearing *in vivo*. These anticoagulants included sulfated polysaccharides and pontamine fast pink.

Following intravenous injection of heparin into humans, Anderson and Fawcett (10) were able to show a sudden fall in surface tension and a clearing of the lipemic plasma. This effect was believed to be due to the formation of a surface active heparin-phospholipid complex, possibly with lecithin, since the *in vitro* formation of such a complex with egg lecithin has been demonstrated. This surface active complex has not been isolated from the blood and further investigations of the mechanism of action of heparin do not tend to support this theory.

By utilizing plasma ultracentrifugation procedures, Graham and his associates (11) have been able to demonstrate that the injection of heparin can markedly alter the lipoprotein spectrum of human plasma. Heparin acts especially to decrease the concentration of those lipoprotein aggregates in the Sf 35-100 range; those in the lower Sf range are less consistently affected. A further substantiation of this effect and its relation to atherosclerosis was reported by Gofman (12) who stated that "the desirability of a pharmacologic approach to the lowering of the Sf 12-100 lipoprotein level is self-evident, if we accept

the hypothesis that serum lipoproteins represent the source of atheroma lipids. Following heparin, there is a reduction in levels of lipoproteins of very high Sf classes (above Sf 20) with a transitory increase in the intermediate classes (Sf 10-20). The Sf 10-20 class may also decrease with a rise in the below Sf 10 class. This shift is in the direction of normal interconversion pathways."

Brown (13, 14) has noted that the negatively charged anticoagulants prevent the development of alimentary lipemia in normal rats absorbing olive oil at a rate sufficient to produce such lipemia. Furthermore, an injection of protamine sulfate, an established antagonist of heparin, into these anticoagulant-treated fat absorbing rats inhibits and reverses the effect of heparin with the resultant appearance of an alimentary lipemia within a few minutes. These observations are based on the fact that heparin is one of the most negatively charged organic compounds formed within the body, and it is suggested that the anti-alimentary lipemic activity of heparin is due to the influence of its negatively charged sulfate groups. This also appears to hold for sulfated dextran and pontamine fast pink. Protamine, being one of the most positively charged proteins, therefore has a great affinity for heparin and can inhibit and reverse its action.

In further attempts to determine the site of action of heparin and the nature of the clearing action, Anfinsen and his associates (15) perfused rats and dogs with heparinized plasma. Their results indicate that the abdominal and thoracic regions exhibit great clearing activity, with the heart and lungs being the most active organs involved. These experiments also show that tissue extract, heparin, and plasma must be present to produce the clearing factor. This clearing factor, produced by the injection of heparin, is destroyed by heat, high salt concentration, and chymotrypsin digestion. Optimal conditions for clearing factor activity were found to be 40° C. and a pH of 7.4. These properties suggest that the clearing factor is an enzyme. Brown and Kauffman (16) found that a lipemic clearing factor could be prepared *in vitro* from a precursor in plasma, tissue factor of pylorus of mice or rats, and heparin. Furthermore, the *in vitro* clearing factor possesses the same properties as the *in vivo* clearing factor when administered to laboratory animals. From their experiments, they concluded that the tissue factor was probably of the sulfhydryl enzyme class.

Anfinsen and coworkers (15) have proposed the following scheme as the probable mechanism of lipemic clearing:

$$\text{a. Plasma Fraction} \xrightarrow[\text{heparin}]{\text{tissue factor}} \text{clearing factor}$$

$$\text{b. Turbid lipoprotein (high Sf)} \xrightarrow[\text{coprotein}]{\text{clearing factor}} \text{decrease turbidity (lower Sf)}$$

Anfinsen (17) also stated that the intravenous administration of heparin causes the removal of chylomicrons or of abnormal low-density beta lipoproteins both *in vivo* and *in vitro*. The tissue factor involved in the production of the clearing factor is believed to be localized in submicroscopic particles in the heart, lungs, and pyloric mucosa. Serum albumin is considered to be an obligatory component of the clearing factor. This latter concept is in agreement with the work of Gordon (18), whose experiments indicate that purified serum albumin enhances the lipemia clearing reaction probably by binding the fatty acids produced which, if not removed, are capable of inhibiting the reaction. Whole serum was found to enhance the albumin clearing, thereby suggesting that a second factor or "coprotein" is also essential. This clearing factor action may be schematically represented as follows (17):

$$\text{Low density lipoproteins} + \text{albumin} \xrightarrow[(\text{"coprotein"})]{\text{clearing factor}} \text{higher density lipoproteins} + \text{albumin (fatty acid)}_n + \text{glycerol}$$

(+ "solubilized" mono- and diglycerides).

The explanation thus offered is that the low-density beta lipoproteins (Sf 10 and above) are degraded in the direction of beta lipoproteins of higher density. In addition, high-density components of alpha$_1$ lipoproteins are also formed. This suggests that clearing factor action might be a "delipidation" with the production of an "alpha lipoprotein core", or that it might transfer lipid molecules to protein components of plasma with higher densities. The absolute increase in high-density alpha$_1$ lipoproteins with a concomitant decrease in certain low-density lipoproteins in studies performed *in vitro*

on heparinized human plasma further supports the suggestion of an enzymatic conversion of one lipoprotein class to another (19).

In his study of the effects of *in vivo* heparin on plasma esterases and lipemia clearing in dogs, Levy (20) found that a rise in esterase levels was associated with clearing of lipemia. Both of these effects are inhibited by protamine sulfate. The findings of increased tributyrin esterase activity following injection of heparin indicate that the enzymatic breakdown of fat and the subsequent migration, metabolism, or dissolution of constituent fatty acids, glycerol, and/or glycerides constitute the basic mechanism of lipemia clearing. The following evidence is offered in support of this hypothesis: (a) the injection of small doses of heparin in lipemic dogs causes both clearing and a rise in plasma esterase activity; (b) the extent of clearing after *in vivo* injection of heparin is proportional to the degree of esterase activation; (c) both clearing activity and esterase activation are reversed by *in vivo* injection of protamine sulfate and azure A; (d) incubation of post-heparin plasma at 60° C. abolishes both effects; (e) *in vitro* azure A inhibits both effects, while protamine will only terminate clearing; (f) dialysis of post-heparin plasma affects neither clearing nor esterase activation; (g) *in vitro* heparin affects neither clearing nor esterase activation. These observations suggest that clearing factor and esterase activation are the same or interdependent.

Hollett and Meng (21) state that the lipemia clearing factor of post-heparin plasma is lipolytic in nature. Pancreatic lipase in the presence of pre-heparin plasma is also capable of producing clearance *in vitro*, but the mechanisms are not the same since the clearing ability of post heparin plasma and pancreatic lipase are inhibited by different compounds. It is believed that a lipase inhibitor is present in normal plasma, thereby preventing its action under normal circumstances. Also, it is possible that the clearing factor of post-heparin plasma is an esterase capable of splitting the ester linkages in neutral fats composed of long-chain fatty acids.

Overbeek (22) and Engelberg (23) reported that the action of clearing factor both *in vitro* and *in vivo* is not necessarily dependent upon esterases or lipases and that the clearing factor will function in the almost complete absence of both enzymes. The behavior of clearing factor towards various inhibitors of these enzymes, together with the liberation of fatty acids during clearing, indicates that clearing factor might be a different type of enzyme—possibly a lipoproteinase,

which possesses some characteristics of both esterases and lipase without being identical to either.

Korn (24) was able to isolate the clearing factor from acetone extracts of normal rat hearts and to identify it as the enzyme lipoprotein lipase. His work shows that this enzyme exists abundantly in adipose tissue, in moderate amounts in heart, and in lesser amounts in lung and skeletal muscle. To elucidate the mechanism of lipoprotein lipase, and to illustrate its role in chylomicron formation and hydrolysis, Korn (3) presented the following scheme:

Hypothetical Cyclical Mechanism for Fat Transport

Within this scheme, the thought is presented that the low-density beta lipoproteins are intermediates in the conversion of chylomicrons to alpha$_1$ lipoproteins via beta lipoproteins of higher density.

Grossman and Straub (25), in their studies on the fate of intravenously administered fat emulsions in rats, found that with the concomitant administration of heparin there resulted a marked increase in the rate of disappearance of the fat from the blood, and a decrease in the accumulation of fat in the spleen and liver. It is their contention that heparin caused a change in the physical state of the fat. These results were substantiated by the observation that heparin increased the rate of clearance of injected cholesterol in rats (26). A feasible explanation of these findings is that heparin causes the dissolution of chylomicrons and possibly an alteration of the size of lipoproteins. This clearing action of infused fats by heparin has also been confirmed in dogs (27) and man (28).

Although heparin is an effective lipid clearing agent, its anticoagulant potency constitutes a major disadvantage to clinical use for the former purpose. For this reason, the lipid clearing activity of chemically related compounds has been extensively investigated (24-33). Many compounds have been found which possess little or no anticoagulant activity, but which are highly antilipemic. Included

among these substances are Treburon, a sodium metaphosphate of high molecular weight, sulphonated amylose depolymerized, sulphonated saponin, sulphonated tannin, and laminarin sulfate. These synthetic products also appear to exert their effect by producing a clearing factor when administered parenterally, and they are as effective as heparin in their clearing ability. It is interesting to note that Hollister (34) observed a clearing action in hyperlipemic patients following the administration of chlorpromazine. No explanation of the mechanism of chlorpromazine clearing has, as yet, been offered.

With the knowledge that cholesterol metabolism is of primary importance in atherosclerosis, various studies have been made of the effect of thyroid and estrogens in the treatment of this condition. It has long been known that hypothyroid states are frequently associated with hypercholesterolemia, and that in males under age forty there is a greater incidence of myocardial infarction due to atheromata than in females of comparable age. Therefore, it was postulated that the administration of thyroid and estrogenic substances might aid lipid metabolism. Pick (35) established the fact that estrogens inhibited coronary atherogenesis and also caused regression of previously produced coronary lesions in the chick despite the continued feeding of cholesterol. This investigator promulgated the idea that estrogens may protect the coronary vessels by the changes occurring in the cholesterol-phospholipid (C/P) ratio, due largely to an increase in lipid phosphorus levels (36). The major disadvantage of estrogen therapy is the production of feminine characteristics in the male. Stamler (37) has shown that with the concomitant administration of androgen and estrogen this unwanted effect is either reduced or eliminated.

A comparison of the activity of heparin and estrogen reveals several points of similarity (38): (a) both decrease the levels of beta lipoprotein; (b) both decrease the C/P ratio; (c) both generally reduce the levels of all serum lipids; and (d) estrogen increases the level of alpha lipoprotein; whereas, heparin produces varying changes in the level of this serum component.

Other investigations indicate that estrogen may inhibit the synthesis and mobilization of cholesterol fractions in the liver and other tissues thereby inhibiting lipid deposition (39). The effectiveness of estrogen may be due to a direct increase of the stability of plasma lipids and lipoproteins, or to a reduction of lipid synthesis caused

by the release of a pituitary factor. This pituitary effect is also reported by Kinsell (40) who postulates the existence of a pituitary factor, "adipokinen", which tends to mobilize fat from the liver, and possibly accelerate fat combustion indirectly.

Of the estrogenic substances studied, estradiol, estrone, and estriol were all found to have similar effects while stilbesterol, progesterone, and other chemically related substances did not affect lipid metabolism (35-42).

Ranney (42) and Cook (43) have recently reported that certain synthetic steroids will also affect lipid metabolism. Methoxy-methyl-estratriene-diol (SC-6924) has been shown to increase the plasma phospholipid concentration, the turnover rate and specific activity of hepatic phospholipids in cockerels. Experiments with 17-alpha-methyl-17-hydroxy-5(10)-estren-3-one (SC-6582) show that this compound has approximately 11 to 40 per cent of the activity of esterone in depressing the plasma C/P ratio in cholesterol fed cockerels; whereas, its estrogenic effect based on uterine growth in mice is less than 1 per cent of that of estrone. Further studies must be made to determine the clinical usefulness of these steroids in the treatment of human atherosclerotic conditions.

It is an established fact that the thyroid hormone accelerates the rate of all metabolic processes in the body; this includes mobilization and oxidation of fat. Administration of thyroid produces a considerable lowering of the C/P ratio and a generalized lipotropic action (39). The following possible mechanisms have been offered in regard to the lipotropic activity of thyroid: (a) it affects atherosclerosis by influencing the tissue accumulation of cholesterol, rather than by an effect on hyperlipemia; (b) there exists a specific depressing action of the hormone on plasma lipids; (c) the hormone decreases the permeability of intimal endothelium to cholesterol; (d) the hormone increases tissue cytochrome.

Strisower and her associates (44) report that administration of thyroid in high doses over a short period of time caused a fall in the levels of cholesterol and of Sf 0-12 and Sf 12-20 lipoproteins in the plasma. With lower doses and longer periods of time, a considerable fall was noted, but an "escape" phenomenon became apparent and the lowered lipoprotein and cholesterol levels gradually returned to prethyroid treatment levels. The hypothesis was advanced that this "escape" phenomenon was due to a cessation of the production

of endogenous thyroid, with the result that the exogenous thyroid was not appreciably in excess of the amount of hormone available before such treatment. This "escape" phenomenon has been prevented by administering considerably larger doses of exogenous thyroid.

While establishing the fact that hyaluronidase, hyaluronic acid, partially depolymerized hyaluronic acid and desoxycorticosterone cause the release of clearing factor similar to that of heparin, Seifter and Baeder (6) also discovered that cortisone and stress would release a clearing factor inhibitor, which in subsequent work has been termed Lipid Mobilizer (LM).

Lyophilized dialyzates of plasma obtained from dogs, rats, and horses receiving cortisone contained LM which markedly elevated plasma levels of free and esterified cholesterol, lipid phosphorous and total fatty acids (45). In hypophysectomized animals, cortisone injection failed to cause a release of LM, thus establishing that an intact pituitary is essential for the liberation of LM. Weekly injections of LM caused a marked depletion of fat from both subcutaneous and internal depots in dogs.

LM produces hyperlipemia when injected into intact animals, presumably by inactivating lipoprotein lipase. LM, tentatively identified as a peptide (46) and isolated from the posterior pituitary of hogs (47), possesses activity comparable to that of LM isolated from plasma dialyzate. LM of pituitary origin induced hyperlipemia in adrenalectomized and hypophysectomized rats due to either inactivation of fat depots or to inhibition of lipoprotein lipase.

Since LM is obtained only from animals with intact pituitaries and induces hyperlipemia in the absence of either the adrenals or the pituitary, it may be assumed to be the mediator through which such stressors as protamine, diisopropylfluorophosphate and pyrogens act as hyperlipemic agents (48).

In elucidating the role of LM, the most significant observations made were that LM elevated plasma fatty acids in hepatectomized rats and that hypertriglyceridemia was not associated with corresponding elevations in cholesterol and lipid phosphorous (49). Seifter and Baeder also observed that LM mobilized triglycerides from the fat depots and that the liver determined the subsequent concentration of lipids in the blood.

In clinical studies, Zarafonetis and associates (50) found that the intravenous administration of LM to subjects on a low fat diet

resulted in a remarkable increase in plasma levels of cholesterol, fatty acids, and lipid phosphorous. This effect was sustained as long as the injections were continued. After LM administration was terminated, however, the lipid values gradually declined to preinjection levels in a week or two. In addition to a sustained hyperlipemia, LM also causes an increase in urinary and fecal cholesterol excretion.

Meals of glucose or cream, but not of amino acids, were found to block the hyperlipemic response to intravenous LM (51). Triglyceride mobilization follows LM administration, but prefeeding of glucose apparently enables the liver to metabolize the lipids presented to it, thereby preventing a peripheral hyperlipemia. From these studies, it was postulated that in patients on a high fat diet a lipid removal or clearing mechanism had been activated and that this somehow negated the LM potential. Such an interpretation depends on the existence of a hormonal system for lipid mobilization-lipid deposition, analogous to the glucagon-insulin mechanism.

Steiger (52), speculating upon the possible role of LM in the treatment of atherosclerosis, posed the question as to whether the high plasma lipids give rise to additional deposition of lipid in arterial walls, or whether the administration of LM mobilizes the lipids from atheromata as well as from fat depots. Seifter, Baeder, and Ziliken (53) have found that the administration of LM to rabbits on standard Anitschkow diet did not aggravate the experimental atheromatous lesions, and LM administered to rabbits on a fat-free diet did not initiate such lesions.

Summary

Heparin has the ability of clearing alimentary lipemia and the lipemia associated with intravenous infusion of fats and cholesterol. The lipid clearing effect of heparin is mediated by the production of a clearing factor in the plasma. Clearing factor has been identified as the enzyme lipoprotein lipase, which appears to convert macromolecular low-density beta lipoproteins to small molecule high-density alpha lipoproteins. Various chemical analogs of heparin have been shown to produce a lipid clearing action identical to that manifested by heparin. Experiments with these analogs indicate that anticoagulant activity and antilipemic activity are independent properties.

Estrogens and several synthetic estrogenic compounds reduce the cholesterol/phospholipid (C/P) ratio, increase the lipid phosphorous

levels, and alter the synthesis and mobilization of cholesterol fractions thereby inhibiting lipid deposition. The administration of thyroid also results in a decrease in the C/P ratio, similar in nature to that produced by estrogens, and a generalized lipotropic action in the tissues.

LM, a peptide derived from the posterior pituitary, induces hyperlipemia and lipid mobilization. The source of the elevated plasma lipids has been demonstrated to be the perirenal, omental, subcutaneous, and mesenteric fat depots. The weight loss and depletion of fat depots which occurs in animals after high doses of LM indicates that fats undergo catabolism, or excretion, or both, rather than mere transportation and redeposition. Further work is necessary to clearly delineate the exact role of Lipid Mobilizer in atherosclerosis.

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SELECTED ABSTRACTS

Chemicals and Antibiotics as Additives or Residues in Food. Roe, R. S. *Am. J. Pub. Health 48:*1498 (1958). The problems concerning chemicals and antibiotics present in food as additives or residues are complex and have great public health significance. The questions as to safety usually do not concern acute toxicity but chronic toxicity which is more subtle and difficult to appraise. The author discussed several of the problems.

Chemicals may be added inadvertently to food as residues from pesticide applications or from sanitizing treatments of plant equipment, or they may be deliberately added for some real or fancied improvement. The Pesticide Amendment to the Food, Drug and Cosmetic Act provides a procedure for establishing safe tolerances for residues of pesticide chemicals in raw agricultural products. Several hundred tolerances have been established.

Coal tar colors are a class of chemical additives, 18 of which were originally listed as harmless and suitable for use in food. Three of these have since been delisted and four others are in the process of being delisted. The current trend is toward that of establishing safe tolerances for each coal tar color since it is now felt that harmlessness and safety must be related to the quantity used.

The Food, Drug and Cosmetic Act prohibits the addition to food of any poisonous or deleterious substance unless the addition is required in the production of the food or cannot be avoided in good manufacturing practice; then, safe tolerances may be established. This provision of the law is not adequate because the status of many substances as to their poisonous or deleterious proclivities may not be known and, secondly, no additive is permitted unless it is necessary. The latter provision does not allow for additives that may be desirable to improper nutritive values, preserve color or flavor, or in some other way serve a useful purpose. The author indicated that the Department of Health, Education, and Welfare felt that the principles which should govern the addition of chemical additives to food are: the intended use would be shown to be safe to long-term as well as short-term consumption, the addition of poisonous or deleterious substances should not be permitted at all unless for a purpose beneficial to the consumer, and the right to appeal a decision should be ensured.

With regard to antibiotics, the author pointed out that residues may occur in food derived from animal sources as a result of the use of the antibiotics in the treatment of disease of the animal as well as from its use as a growth stimulant for the animal. Penicillin, for example, even in trace amounts, may cause serious reactions in individuals who are sensitive to the drug. Such residues may occur, for example, in milk following the treatment of cows for mastitis. This problem has been controlled largely through the certification required for preparations for the treatment of mastitis. Antibiotics, estrogenic hormones, and other chemicals added to animal foods have largely been controlled by interpreting such use as a "new drug" use. A new drug use requires submission by the promoter of evidence that the drug as used is safe. In these uses, the evidence of safety must include evidence that residues are absent from the food products derived from the treated animals.

Antibiotics have been proposed as preservatives on raw agricultural products, fish, meat and poultry, and other foods. Tolerances have been established for residues of chlortetracycline and oxytetracycline at 7 ppm in or on raw poultry. This was permitted because it had been shown that such residues were destroyed during the cooking of the poultry.

The author noted that since the writing of this article the Food, Drug and Cosmetic Act has been amended to require pretesting of additives to foods to establish their safety.

Clinical Studies With Chlorpropamide. Heinsen, H. A. Presented before the Conference on Chlorpropamide and Diabetes Mellitus, The New York Academy of Sciences, Section of Biology, Sept. 25-27, 1958. The author reported the results of clinical experiences with chlorpropamide in more than 50 patients with diabetes mellitus. As with carbutamide and tolbutamide, chlorpropamide was found to be more effective in the treatment of diabetes millitus in the older-aged patient. Younger patients were generally not suitable subjects for treatment with these three sulfonylureas.

At the same dosage level, it was found that the hypoglycemic effect of chlorpropamide was greater than that of either carbutamide or tolbutamide. The excretion of chlorpropamide has been found to

be very slow. It felt that this factor might explain the greater and more prolonged effectiveness of chlorpropamide as compared with the other sulfonylureas. The average range of maintenance doses for chlorpropamide was found to be from 125 to 500 mg. a day. Initial doses of 1000 to 1500 mg. were given for only 4 or 5 days and then the dosage was reduced to maintenance levels. It was observed that chlorpropamide could satisfactorily control the diabetic state in patients who had been receiving depot dosages of insulin as high as 40 units a day.

Toxic side effects were minimal. Several patients manifested gastrointestinal disturbances with doses of 500 mg. three times a day. However, these symptoms disappeared as the dosage was reduced to maintenance levels. No hypoglycemic episodes occurred nor was any evidence observed indicative of damage to the liver, kidneys, or hematopoietic system. One patient with hepatitis and jaundice recovered completely while under chlorpropamide therapy.

Treatment of Gastric Disturbances With New Wafer Form of Medication. Hufford, A. R. *J. Am. Geriat. Soc. 6:766* (1958). Gastro-intestinal disorders referable to hyperacidity occur commonly in elderly patients. The monotonous, rigid diets often required cause the development of resentment toward them on the part of some patients. Because of this, a new medicated wafer was administered to 54 patients, ranging in age from 33 to 79 years. The flavored wafer (Biscule) contained Kolantyl plus ingredients to provide about 45 calories and 0.45 Gm. of protein per wafer.

The chief disorders among the patients treated were: peptic ulcers, functional gastric disturbances, and gastro-intestinal irritation frequently associated with peptic ulcers. Elderly patients received 1 or 2 wafers, one to two hours after each meal. In younger patients, the wafers were used as a supplement to regular Kolantyl medication for between-meal feedings and bed-time snacks. The period of the study reported was 6 to 12 weeks.

Symptomatic improvement was reported in 92.6 per cent of the patients. Only 2 of the 54 patients complained of undesirable features of the wafer: one objected to the taste and the other had a recurrence of allergy to milk. No undesirable anticholinergic effects of the drug were observed.

The author concluded that the therapeutic effectiveness of Kolantyl was unaltered by its incorporation in the new wafer form. In fact, the high degree of patient acceptability increased the therapeutic effectiveness of the drug. In addition, the nutritive value of the wafer provided more than just medication for the between-meal snacks. Also, the bulk furnished by the wafer aided in counteracting and absorbing free acid in the stomach.

A Study of the Potency Stability of Poliomyelitis Vaccine. Perkins, F. T., and Yetts, R. *Brit. Med. J.* No. 5113:31 (1959). The authors performed a study of the stability of poliomyelitis vaccine at three different temperatures of storage. This study was designed to attempt to determine a realistic expiration date for the vaccine. The present expiration is usually given at six months if storage is at 4° C.

The author stored three batches of vaccine, two British and one American, at 4° C., 21° C., and 31° C. and then evaluated the antigenic potency of each of the three strains composing the vaccine. All three batches contained MEF-1 and Saukett as the 2 and 3 type strains, respectively. The type 1 strain was Brunenders in British and Mahoney in American batches.

Following storage at 4° C. for 12 months, there was no evidence of loss of potency in any of the strains of the three batches. One batch stored at 4° C. showed no loss after 21 months. Following storage at 21° C., strains 2 and 3 showed no loss of potency after 100 days. However, strain 1 showed some loss after 40 days at this temperature and an appreciable loss after 100 days. At the highest temperature of 31° C., there was considerable loss in potency of type 1 after 40 days, less loss of type 2, and little or no loss of type 3. However, after 100 days at 31° C., the activity of all three types was completely lost.

Therefore, the authors concluded that poliomyelitis vaccine may be safely stored for 12 months at 4° C. or, probably, within the range of 0° C. to 10° C. Because of the reduced stability at room or higher temperatures, it is important that transportation be carried out within a short period of time. In tropical areas, it would appear that transportation should not be undertaken unless the vaccine is refrigerated.

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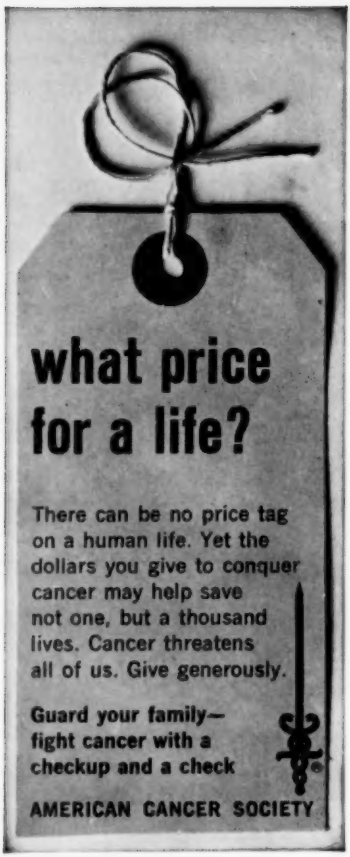
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